| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/518,390 | LOUVAIN ET AL. | |
| | Examiner | Art Unit | |
| | Marsha M. Tsay | 1656 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *or interview of July 23, 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *3,9,10 and 18-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3,9,10 and 18-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *20090723* .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

This Office action is in response to the interview conducted with Applicants' representative, Dr. Vincent Shier, on July 23, 2009. Dr. Shier explained the difference(s) between the instant invention and the Himmelspach et al. reference. Dr. Shier further noted that Himmelspach et al. does not qualify as anticipatory art as 102(e). Upon consideration of Applicants' position and in further review of the Himmelspach et al. reference, it is believed that the Himmelspach et al. is more applicable as a 103(a) reference.

Prosecution on the merits of this application is reopened on claims 3, 9-10, 18-22, which are considered unpatentable for the reasons indicated below.

Applicants' arguments have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous Office actions are hereby withdrawn.

Claims 1-2, 4-8, 11-17, 23-38 are canceled. Claims 3, 9-10, 18-22 are currently under examination.

Priority: The request for priority to FRANCE 0208299, filed July 3, 2002, is acknowledged.

**Objections and Rejections**

Claims 3, 18-21 are objected to because of the following informalities: in claims 3, 18-21, there should be an article, i.e. "A", at the beginning of each claim. Appropriate correction is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3, 9-10, 18-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 3, 9-10, 18-22 are rejected under 35 U.S.C. 112, first paragraph, for a lack of structure.

The court of Appeals for the Federal Circuit has recently held that such a general definition does not meet the requirements of 35 U.S.C. 112, first paragraph. " A written description of an invention involving chemical genus, like a description of a chemical species, requires a precise definition, such as be structure, formula {or} chemical name, of the claimed subject matter sufficient to distinguish it from other materials." *University of California v. Eli Lilly and Co.,* 1997 U.S. App. LEXIS 18221, at *23, quoting *Fiers v. Revel,* 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). The court held that " in claims involving chemical materials, generic formulae usually indicate with specificity what generic claims encompass. One skilled in the art can distinguish such a formula fro others and can identify many of the species that the claims encompass. accordingly, such a formula is normally an adequate description of the claimed genus. In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA,' without more, is not an adequate written description of

the genus because it does not distinguish it from others. One skilled in the art therefore cannot, as one can do with a fully described genus visualize the identity of the members of the genus".

Here, Applicants are reciting claims drawn to Factor X/Xa analogues having only the structural limitation of a 6-mer (i.e. SEQ ID NO: 9). There is no other structural limitation recited besides SEQ ID NO: 9. Additional information regarding the structure of the instant Factor X/Xa analogues is requested.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 22 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 22 recites procoagulant medicinal product. It is unclear what is meant by "procoagulant medicine product", i.e. a composition, etc. Further clarification is requested.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 3, 18, 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Himmelspach et al. (US 6573071; previously cited).

For examination purposes, claim 3 has been interpreted as a Factor X analogue comprising the sequence Val-Pro-Arg-Ala-Val-Gly (SEQ ID NO: 9). Therefore, any reference disclosing a Factor X analogue comprising at least instant SEQ ID NO: 9 is believed to be relevant art.

Himmelspach et al. disclose a Factor X analogue, having a modified processing site, comprising the sequence Gly228 to Ile235 having the sequence Gly228-R6-R5-R4-R3-R2-Arg234-R1 (col. 83, see also SEQ ID NO: 27), wherein

a) R1 is an amino acid selected from the group consisting of Ile, Val, Ser, Thr, and **Ala**,

b) R2 is an amino acid selected from the group consisting of **Pro**, Gly, Lys, and Arg,

c) R3 is an amino acid selected from the group consisting of Phe, Lys, Met, Gln, Glu, Ser, **Val**, Arg, and Pro

Therefore, Himmelspach et al. disclose a Factor X analogue comprising the sequence Gly228-R6-R5-R4-**Val232-Pro233-Arg234-Ala235-Val236-Gly237**, wherein the amino acids in bold correspond to the instant thrombin-cleavable sequence Val-Pro-Arg-Ala-Val-Gly. Himmelspach et al. also disclose a preparation comprising said Factor X analogue having a processing site as noted by the sequence noted above, therefore said preparation would be a medicinal product (col. 84 lines 60-67). Himmelspach et al. do not explicitly teach a Factor X analogue comprising Val-Pro-Arg-Ala-Val-Gly (instant SEQ ID NO: 9).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a Factor X analogue, having a modified processing site, comprising Gly228-R6-R5-R4-**Val232-Pro233-Arg234-Ala235-Val236-Gly237**, wherein the amino acids in bold correspond to the instant sequence Val-Pro-Arg-Ala-Val-Gly (SEQ ID NO: 9) (claims 3, 22).

The motivation to do so is given by Himmelspach et al., which disclose Factor X analogues can comprise a modified processing site having an amino acid sequence formula that encompasses instant SEQ ID NO: 9.

While Himmelspach et al. do not specifically teach a Factor Xa analogue, this analogue is within the scope of Factor X analogues disclosed by Himmelspach et al. since upon cleavage of the Factor X analogue of Himmelspach et al. as noted in the paragraph above, one of ordinary skill would obtain a Factor Xa analogue since the Factor X analogue of Himmelspach et al. can comprise instant SEQ ID NO: 9 (claim 18). It should also be noted that the phrase "can be obtained by cleavage of a Factor X analogue by thrombin" is also describing a property of the factor X analogue which would be present as long as SEQ ID NO: 9 is encompassed within the Factor X analogue.

Regarding Applicants' arguments that Himmelspach et al. fail to disclose or suggest a factor X analogue having the sequence Leu-Thr-Arg-Ile-Val-Gly (instant SEQ ID NO: 1) of the activation site of native factor X replaced with the sequence Val-Pro-Arg-Ala-Val-Gly (instant SEQ ID NO: 9) with sufficient specificity and that the artisan would have no reason to select this factor X analogue from the extensive list of alternative factor X analogues, much less an expectation of the beneficial results flowing from the same. Indeed, when a compound is not specifically named, but instead it is necessary to select portions of teachings within a reference and combine them, as in Himmelspach et al., anticipation can only be found if the classes of [possibilities] are sufficiently limited or well delineated. *Ex parte A*, 17 USPQ2d 1716 (Bd. Pat. App & Inter. 1990). If one of ordinary skill in the art is able to "at once envisage" the specific

compound within the generic chemical formula, the compound is anticipated. Typically, one of ordinary skill in the art must be able to draw the structural formula or write the name of each of the compounds (or in this case, each factor X analogue) included in the generic formula before any of the compounds can be "at once envisaged." *In re Petering,* 301 F.2d 676, 133 USPQ 275 (CCPA 1962). Applicants further assert that when looking to see whether there would even be a motivation to select the specifically claimed factor X analogue, the artisan may look to the preferred analogues disclosed by Himmelspach et al. None of the preferred analogues disclosed by SEQ ID NOS: 29-74 of Himmelspach et al. comprises the specific combination wherein R1 would be Ala, R2 would be Pro, and R3 would be Val, which corresponds to the Factor X analogue of the presently claimed invention. Applicant's arguments have been fully considered but they are not persuasive.

Firstly, it should be noted that claim 3 is essentially directed to a Factor X analogue having the sequence Val-Pro-Arg-Ala-Val-Gly (instant SEQ ID NO: 9) at the activation site. Therefore, any reference disclosing a Factor X analogue comprising instant SEQ ID NO: 9 would be relevant art. Since Himmelspach et al. disclose a Factor X analogue having a modified processing site comprising an amino acid sequence formula that comprises instant SEQ ID NO: 9, the Factor X analogue meets the structural limitations recited in instant claim 3 and would therefore be relevant art.

Secondly, it should be noted that the limitation recited in instant claim 18, “cleavage of a Factor X analogue by thrombin," is a descriptive property of the Factor X analogue which would be present as long as SEQ ID NO: 9 is present. Since Himmelspach et al. do disclose SEQ ID

NO: 9 can be encompassed within a Factor X analogue, this limitation of claim 18 would at least be obvious over Himmelspach et al.

Regarding Applicants' comments that none of the preferred analogues disclosed by SEQ ID NOS: 29-74 of Himmelspach et al. (col. 6 lines 10-45) comprises the specific combination wherein R1 would be Ala, R2 would be Pro, and R3 would be Val, which corresponds to the Factor X analogue of the presently claimed invention, Applicants are referred to MPEP 2123. "Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. In re Susi, 440 F.2d 442, 169 USPQ 423 (CCPA 1971)... Furthermore, '[t]he prior art's mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed….' In re Fulton, 391 F.3d 1195, 1201, 73 USPQ2d 1141, 1146 (Fed. Cir. 2004)." In this instance, Himmelspach et al. disclose R1 = Ser, R2 = Thr, R3 = Leu, for processing by Factor IIa; however, this does not preclude that fact that R1, R2, and R3 cannot be Ala, Pro, and Val, since these three residues are disclosed as residues that can be substituted for R1, R2, and R3.

For at least these reasons, the Himmelspach et al. reference is believed to be relevant 103(a) art.

Claims 19-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Himmelspach et al. (US 6573071; previously cited). The teachings of Himmelspach et al. are outlined above. Himmelspach et al. further disclose nucleic acid molecules, expression vectors, and host cells that can be used to express the Factor X analogues disclosed by Himmelspach et

al. (col. 17-28). Himmelspach et al. do not explicitly teach a nucleic acid molecule encoding the thrombin-cleavable sequence Val-Pro-Arg-Ala-Val-Gly (SEQ ID NO: 9).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare a Factor X analogue having the thrombin-cleavable sequence Val-Pro-Arg-Ala-Val-Gly (SEQ ID NO: 9) as disclosed by Himmelspach et al. by constructing expression plasmids for the preparation of Factor X analogue for expression in host cells (claims 19-21). The motivation to do so is given by Himmelspach et al., which disclose that Factor X analogues having the thrombin-cleavable sequence Val-Pro-Arg-Ala-Val-Gly (SEQ ID NO: 9) can be prepared by constructing expression plasmids followed by transformation into a host cell for expressing a Factor X analogue protein.

The Himmelspach et al. reference is still maintained over claims 19-21 because it is believed to be relevant art for the reasons as noted above.

Claims 9-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Himmelspach et al. (US 6573071; previously cited). The teachings of Himmelspach et al. are outlined above. Himmelspach et al. further disclose Factor X/Xa is an important component of the prothrombinase complex and may be used to treat patient suffering from blood coagulation disorders, i.e. hemophilia (col. 3-4). Himmelspach et al. do not explicitly teach a preparation comprising a Factor X analogue with the thrombin-cleavable sequence Val-Pro-Arg-Ala-Val-Gly (SEQ ID NO: 9) and a method of treating hemophilia utilizing said Factor X analogue.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to administer the Factor X analogue of Hammelspach et al. to a patient for the treatment of hemophilia because Hammelspach et al. disclose Factor X/Xa which exhibits high stability and can be activated to Factor Xa without use of conventional proteases (col. 4 lines 30-35), i.e. modified to have the thrombin-cleavable sequence Val-Pro-Arg-Ala-Val-Gly (SEQ ID NO: 9), can be administered to treat patients suffering from hemophilia (claims 9-10).

The Himmelspach et al. reference is still maintained over claims 9-10 because it is believed to be relevant art for the reasons as noted above.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marsha M. Tsay whose telephone number is (571)272-2938. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Maryam Monshipouri/

Primary Examiner, Art Unit 1656

July 31, 2009